E. W. Adams

Synthesis in the Heterocyclic Series

SYNTHESES IN THE HETEROCYCLIC SERIES

BY

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B. S. University of Illinois, 1919

THESIS

Submitted in Partial Fulfillment of the Requirements for the

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THE GRADUATE SCHOOL

August 12 1920

I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY

SUPERVISION BY Elmer Wade Adams

ENTITLED Syntheses in the Heterocyclic Series

BE ACCEPTED AS FULFILLING THIS PART OF THE REQUIREMENTS FOR

THE DEGREE OF Master of Science

Oliver Kamm
In Charge of Thesis

Geo. D. Beal
Head of Department

Recommendation concurred in*

Committee
on
Final Examination*

*Required for doctor's degree but not for master's

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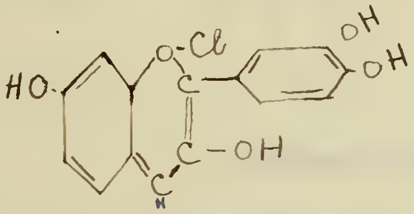
Syntheses in the Heterocyclic Series.

INTRODUCTION

The most important of the naturally occuring dyes are the various pyrones, classified as anthocyanins, xanthones, flavones, etc. Alpha-pyrone, commonly called coumarin, is found in the tonka bean and has also been prepared synthetically.

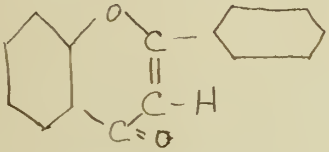
These pyrone derivatives make up a very large class of compounds and form the basis for the various naturally occuring flower pigments. As an example we may mention the anthocyanin that has been isolated from the corn flower. It is called cyanin and, altho it itself has not been synthesized, it has been hydrolyzed by hydrochloric acid, yielding glucose and a product called cyanidin chloride, a compound that has been synthesized. It possesses the following structure:



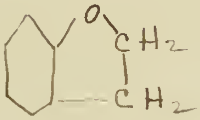
More or less closely related to the flavone group are a number of classes of simpler compounds, namely the coumarans, chromanes, and chromenes. The first two have been synthesized by various methods, as will be shown later, but neither of the two chromenes, alpha or beta, has been made in the laboratory, even tho they are so much more closely related in structure to

the naturally occuring derivatives than are the coumaranes or chromanes as to have been referred to as "the basic substances of the large class of natural dyes, the flavones and their derivatives."

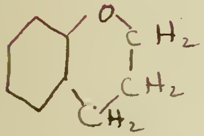
The relationship of these compounds can be seen by comparing the following structural formulae:



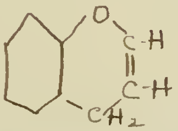
<u>flavone</u>



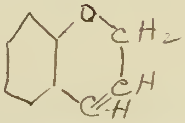
<u>coumarane</u>



<u>Chromane</u>



<u>Alpha-chromene</u>



<u>beta-chromene</u>

The chief point of difference between flavone and its derivatives and the other compounds given is that the former has a ketone group. It will be noted that all are heterocyclic compounds, the hetero atom being oxygen. The flavone has a six-membered unsaturated ring whereas the coumarane and chromane have respectively five- and six-membered saturated rings. The points of striking similarity between the flavones and the

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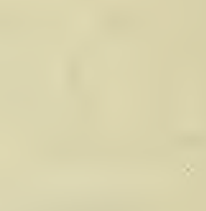

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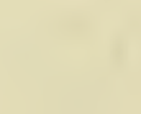

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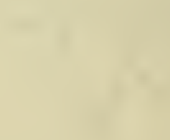

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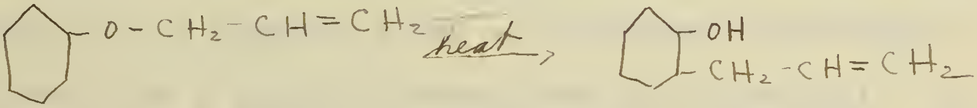
chromenes are that both have not only six membered rings, but that these rings are unsaturated.

The present investigation has been limited for the most part to a study of heterocyclic ethers in the above named groups, especial emphasis being placed upon an attempt to devise some method whereby the beta-chromene could be synthesized in the laboratory.

HISTORICAL

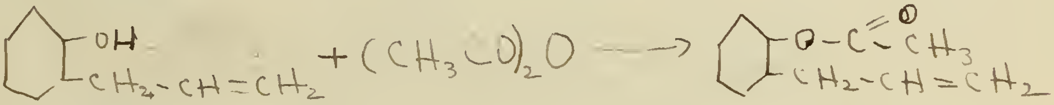
It has been shown that an easy general method to prepare cyclic ethers is through the ortho-allyl phenols. Claisen[3] demonstrated that the ortho-allyl phenols can be prepared easily by the rearrangement of the corresponding allyl ethers, the general reaction being as follows:



Claisen[4] also used pyridine hydrochloride to convert the ortho-allyl phenols into methyl coumaranes, the reaction being as follows:

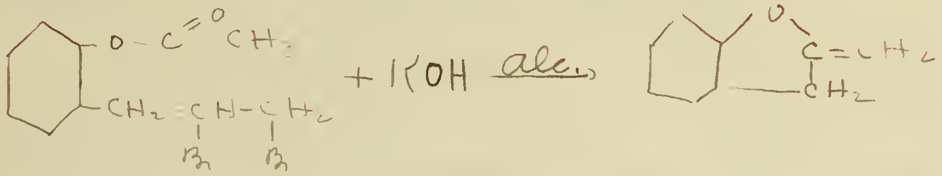
R. Adams and R. E. Rindfusz synthesized the methylene coumaranes readily from ortho-allyl phenols by the following series of reactions:

1. Acetylation of ortho-allyl phenol.



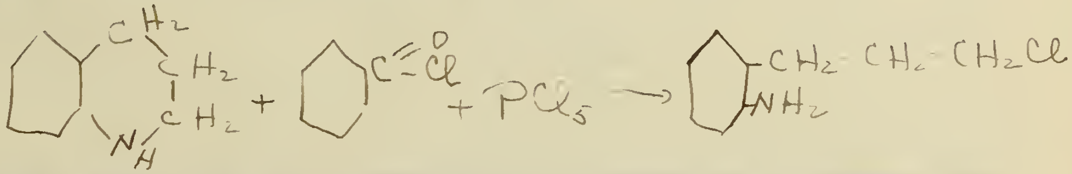
2. Addition of bromine to the double bond.

3. Treatment with alcoholic potash

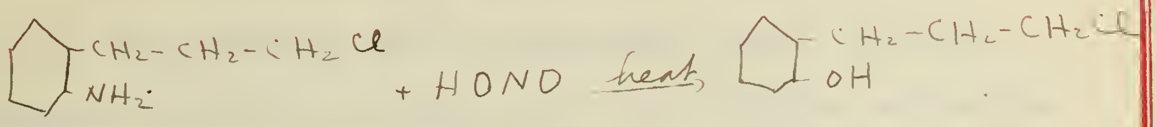


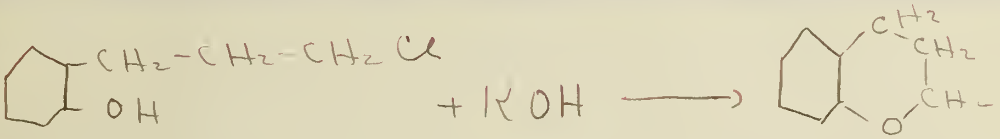
The reaction in the last case has proved to be a general one with the ortho-allyl phenols. In this work[5] they started with the intention of preparing the six membered unsaturated ether or chromene by a similar method used by Kastanecki[6] in the preparation of the flavones; but instead of obtaining the chromene as expected, the last reaction in the synthesis failed to go according to that of the flavones and they obtained the methylene coumarane.

Still other methods of attack upon the problem of synthesizing these compounds have been used. Von Braun and Steindorff[7] prepared the six membered saturated cyclic ether or chromane in their work on the splitting of nitrogen ring compounds. They treated tetra-hydro-quinoline with benzoyl chloride and phosphorus penta-chloride and obtained gamma-chloro-ortho-propyl aniline.



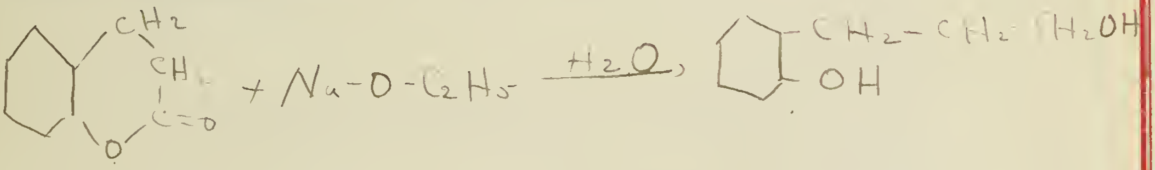
This aniline derivative was diazotized to replace the amino group by an hydroxyl and then the ring was closed by means of alkali, the final product being chromane.



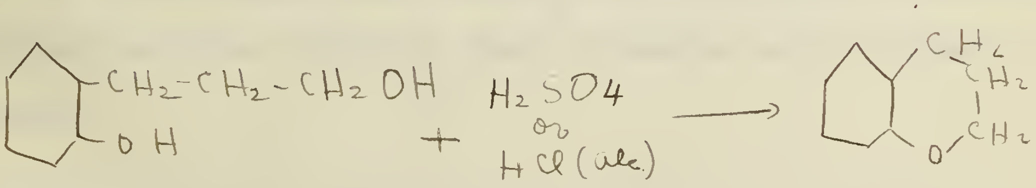


This method however, even at its best, proved to be a rather long, tedious, and poor synthesis.

In 1906 Semmler[8], using his general method for converting lactones to glycols, reduced coumarin with sodium and alcohol to the ortho-gamma-propyl phenol as follows:

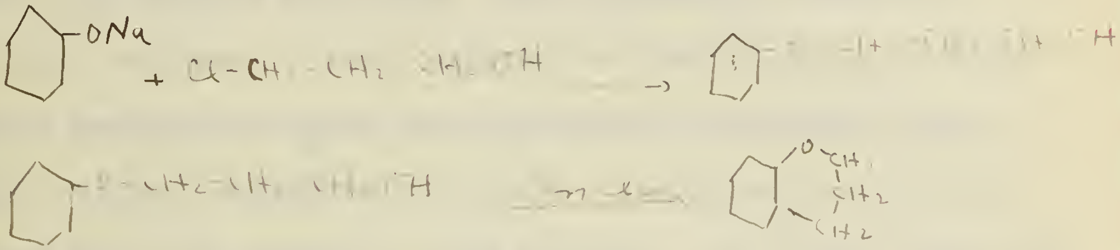


From this he obtained the chromane by dehydration with sulphuric acid or alcoholic hydrogen chloride in a bomb.

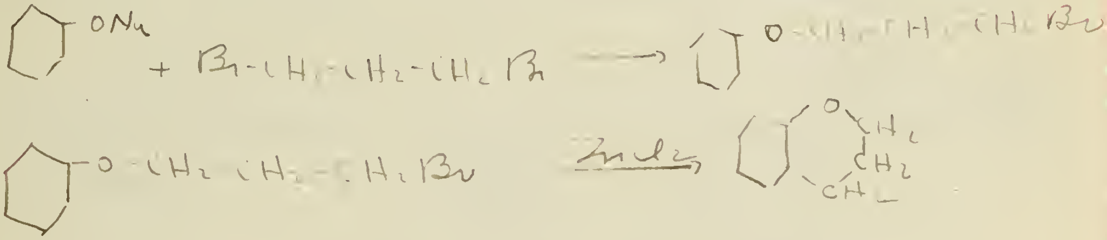


The above were the only methods of preparing chromane that had been published up until 1919. During this year, R. E. Rindfusz[9] prepared chromane by three new methods, as follows:

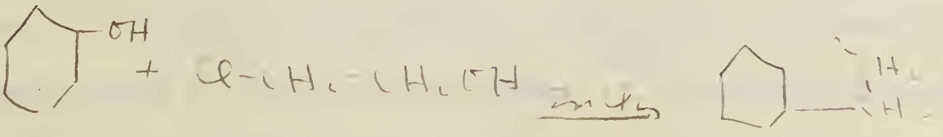
1. Trimethylene glycol monophenyl ether, which is easily prepared from the corresponding chlorohydrine and sodium phenolate, is heated with zinc chloride, the reaction being as follows:

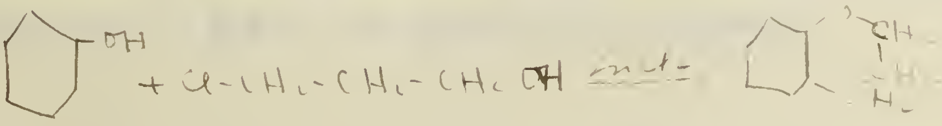


2. Beta-bromo-ethyl phenyl ether and gamma bromo-propyl phenyl ether are converted into cyclic ethers by the action of zinc chloride.



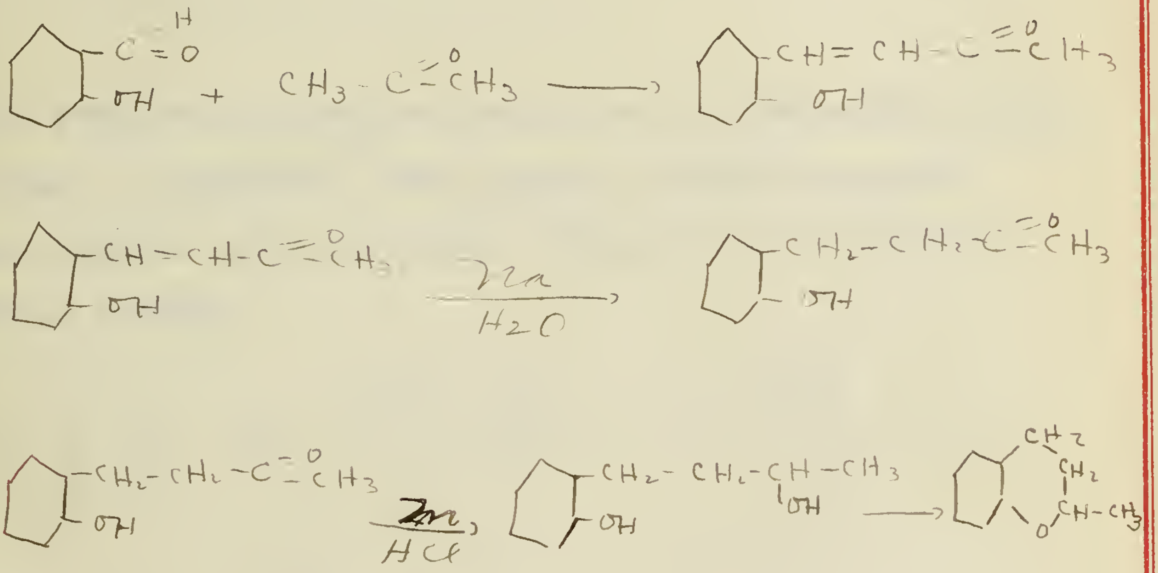
3. Free phenol when heated with ethylene or trimethylene chlorohydrine and zinc chloride gives coumarane and chromane, respectively.



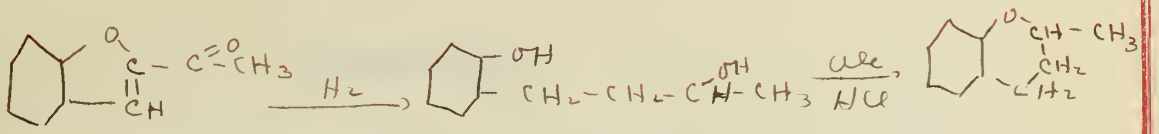


Some work has been done upon other cyclic ethers, a few of the more important examples being noted below:

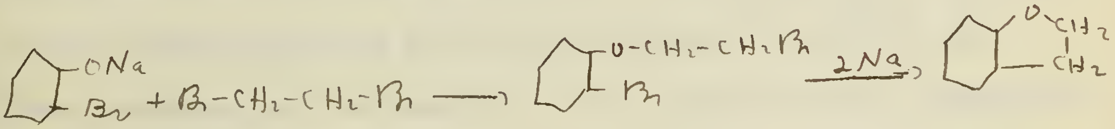
Alpha methyl chromane has been twice synthesized; first, by the use of ortho-gamma-hydroxy-butyl phenol as the intermediate and second, by Harries and Busse[10] who condensed salicylic aldehyde with acetone. They reduced the condensation product with sodium amalgam to give the saturated keto-phenol which, upon still further reduction with zinc and hydrochloric acid, was changed from the ketone to the alcohol, the latter reacting at once to form methyl chromane.



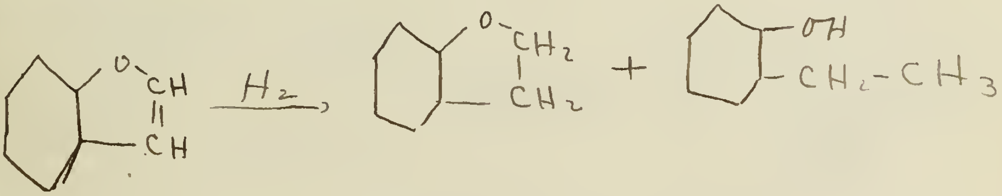
Stoermer[11] prepared and isolated the above intermediate alcohol-phenol used by Harries and Busse[10] by reducing alpha-methyl coumarone. He then closed the ring by means of alcoholic hydrogen chloride to give, the alpha-methyl chromane.



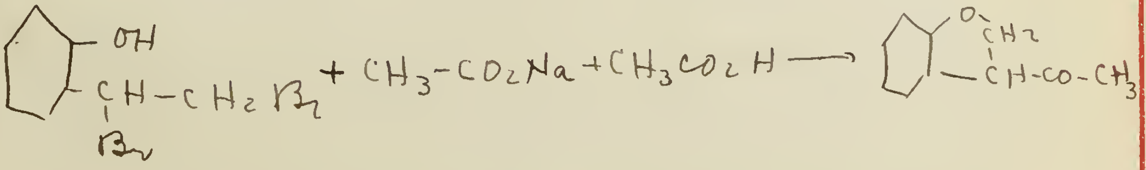
As to the work on coumaranes it may be said that the parent substance was synthesized by Stoermer and Gohl[12] by treating ortho-bromo sodium phenolate with one molecule of ethylene bromide and then adding sodium.



(They also prepared derivatives having one and two methyl groups in the ring.) Alexander[13] had, however, already obtained coumarane together with ortho-ethyl phenol by the reduction of coumarone as follows:

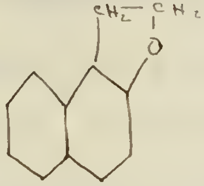


Fries and Moskopp[14] prepared the keto-acetyl derivative by treating ortho 1, 2-dibromo-ethyl phenol with sodium acetate and acetic acid.



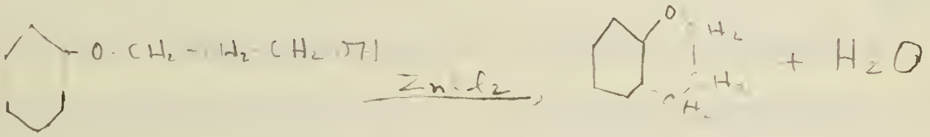
THEORETICAL

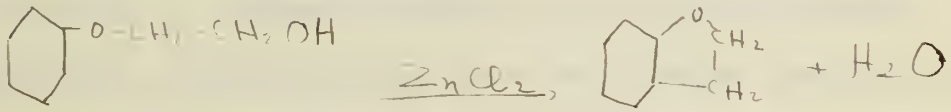
Preparation of beta-Naphthodihydro-furane



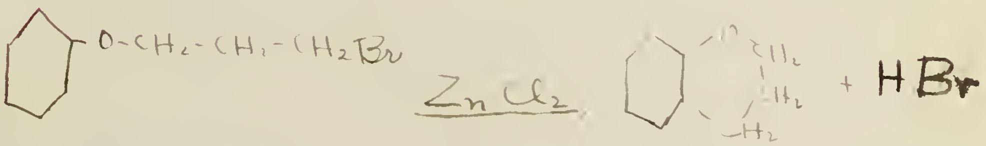
The first part of this investigation was the preparation of the dihydro-furane of beta-naphthol. The work was a continuation of the investigation by R. E. Rindfusz[9] in 1919, who showed that chromane and coumarane can be quite easily prepared by either of the two following methods:

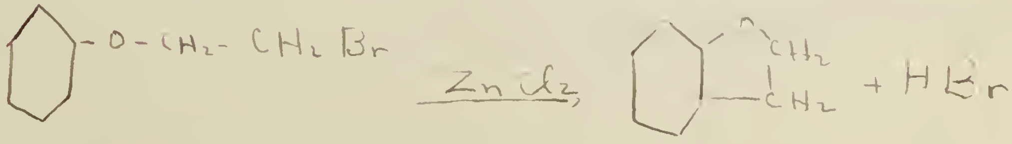
I





II



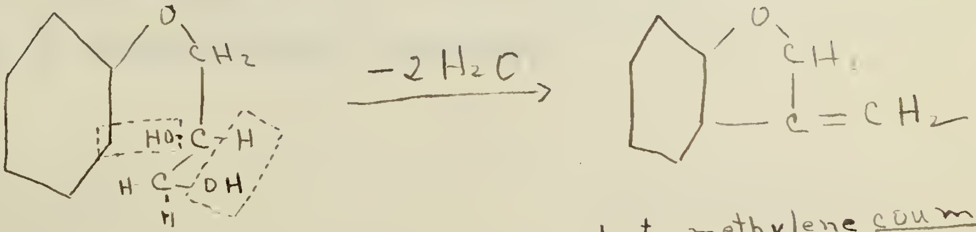


It was thought quite possible that by starting with certain substituted phenols and using the same methods that similar compounds might be prepared. And so at the suggestion of Dr. Rindfusz the attempt was made using the alcohol-ether prepared in the same general investigation[5] from beta-naphthol and ethylene-chlorohydrine, (beta-hydroxyethyl-beta-naphthyl ether). It may be mentioned at this point that phosphorus-pentoxide was used as the dehydrating agent in this case with better results than zinc chloride, as was also found true by others in this laboratory synthesizing similar cyclic phenolic ethers.

Attempted Syntheses to Prove the Structure of C_9H_8O.

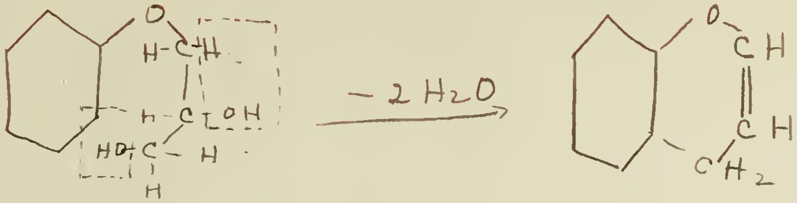
In one of his investigations Dr. Rindfusz obtained a compound, altho only partially pure, from the dehydration by means of phosphorus pentoxide of the ether-alcohol resulting from the treatment of sodium phenolate with glycerol-alpha-mono-chlorohydrin. In this case there were three possibilities of dehydration, as follows:

I



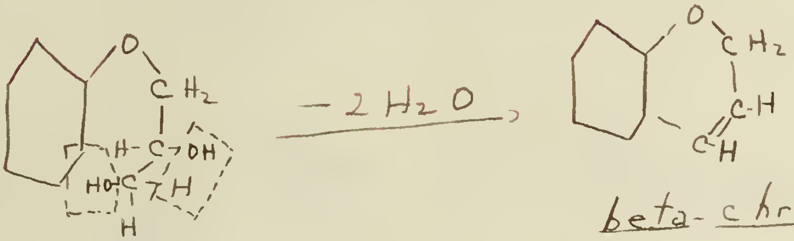
beta-methylene coumarane

II



alpha-chromene

III

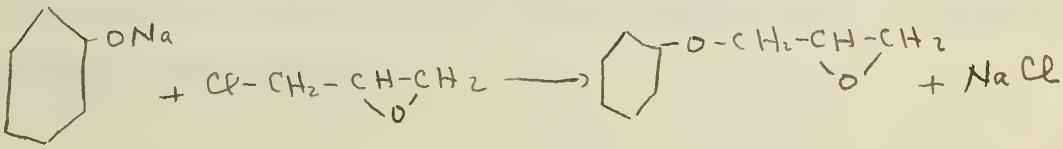


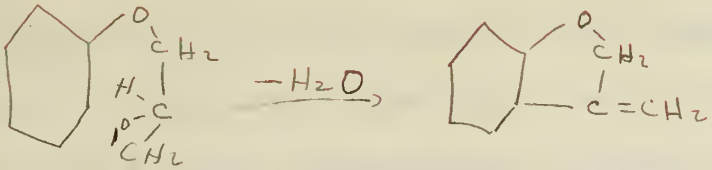
beta-chromene

The general aim of this part of the investigation was to devise some means whereby one or two of the above compounds could be definitely synthesized and their respective constants checked with those of the unknown whose structure was in question. Numerous attempts were made by various methods to synthesize both the beta-methylene coumarane and the beta-chromene but all were unsuccessful in the end, even though one or two did appear quite promising indeed until tried in the laboratory.

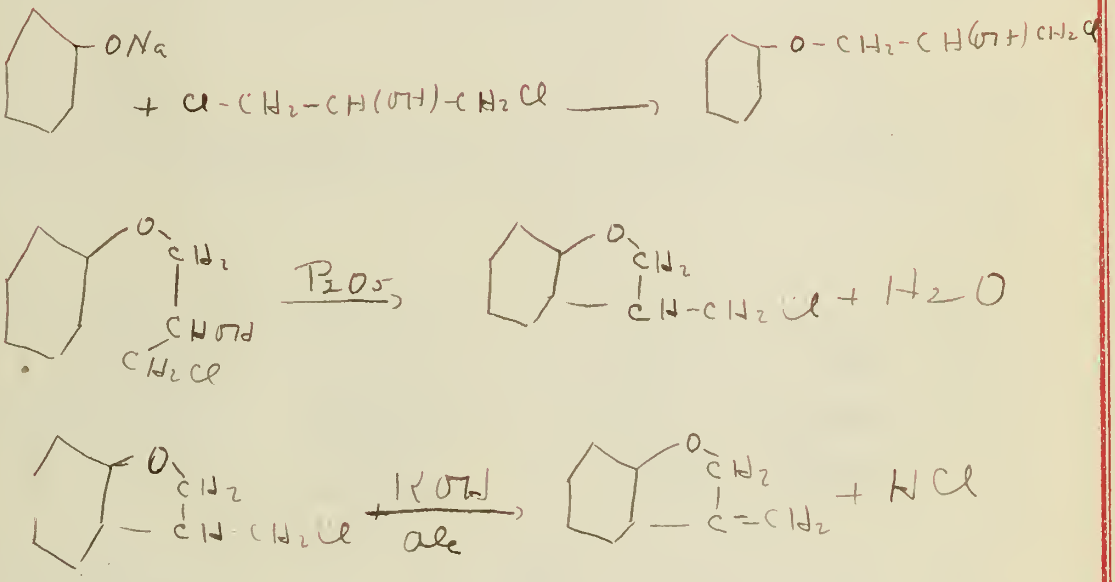
The two following methods[19] were used for the attempted preparation of beta-methylene coumarane:

I





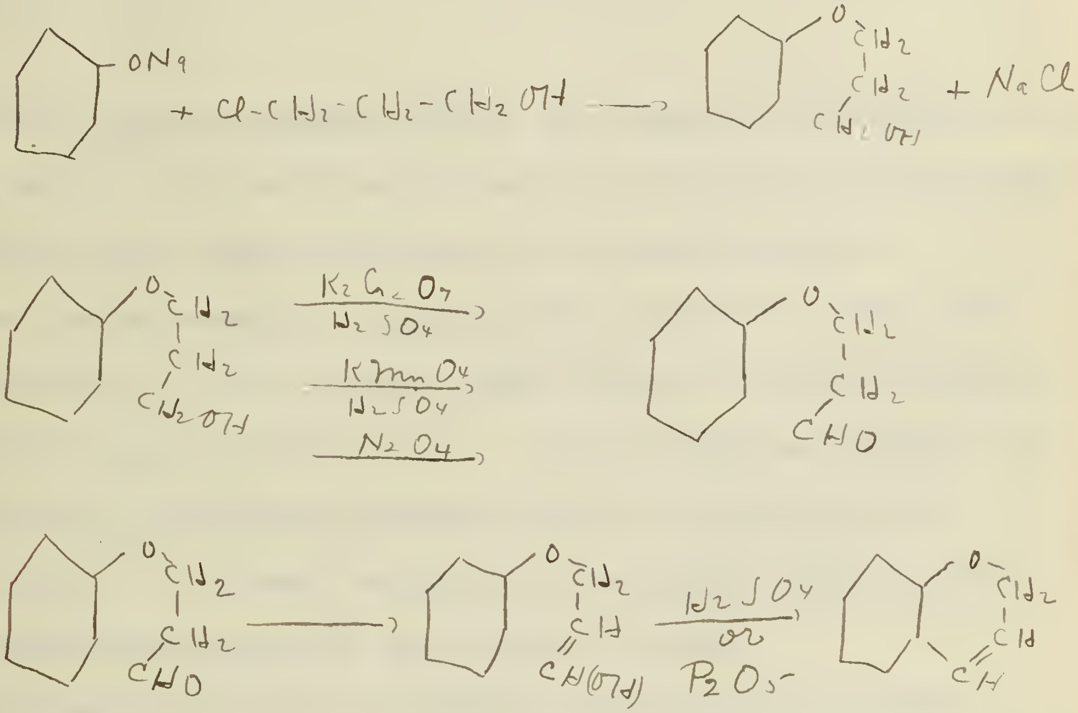
II



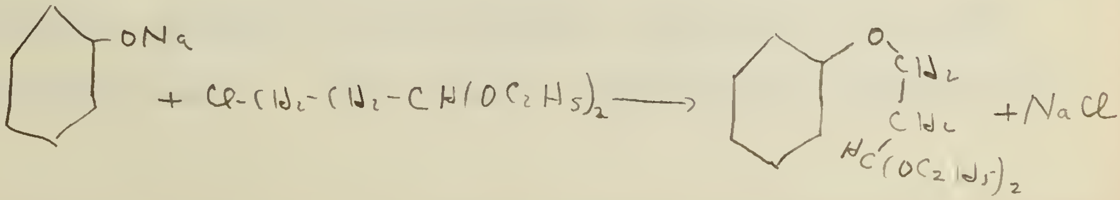
It may be mentioned here that in the treatment of sodium phenolate with 1,3 dichlorohydrine, ~~that~~ the tendency was quite marked under all conditions of concentration and temperature tried for two mols of the phenolate to react with dichlorohydrine to give the di-phenyl ether, the latter being isolated and analysed.

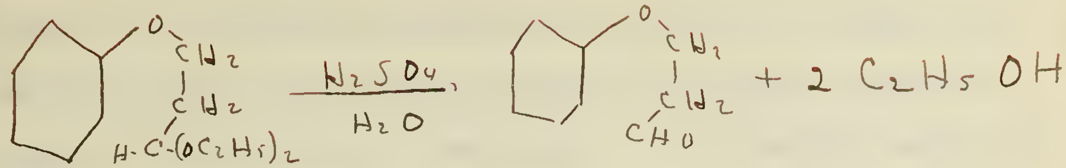
In the attempted preparation of beta-chromene the following general methods were employed:

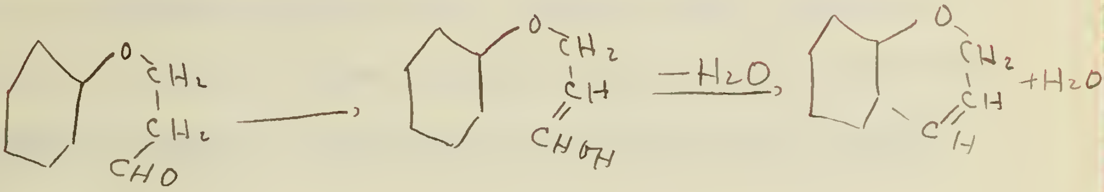
I. Preparation of the alcohol-ether (gamma-hydroxy-propyl-phenyl-ether) by the method previously used by Rindfusz,[9] the oxidation of this to the corresponding aldehyde, and the dehydration of the enolic form of the latter by use of phosphorus pentoxide as follows:



II. The second line of procedure was suggested by Dr. O. Kamm and consisted in the preparation of beta-chloro-propanal acetal from acrolein, the treatment of sodium phenolate with this in alkaline solution, the hydrolysis of this product to get the aldehyde, and the dehydration of the enolic form as follows:







The beta-chloro-propanal-acetal was prepared according to the method of Wohl[16] but could not be made to react with sodium phenolate to split out sodium chloride as we should expect.

Since the beta-chloro compound above failed to react with sodium phenolate, it was thought that perhaps the corresponding bromo or iodo acetal would do so. Accordingly an attempt was made to prepare beta-bromo propanal-acetal according to the method of Nef.[17] A small amount of the product was obtained, but an insufficient quantity with which to work.

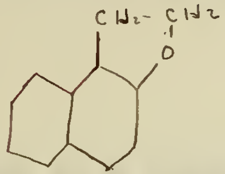
Two attempts were made to prepare the beta-iodo acetal, both being by replacement of the chlorine atom by iodine in the previously prepared compound. The first attempt, which was wholly unsuccessful, consisted in heating for ten hours, at one hundred degrees in a sealed tube, molecular amounts of beta-chloro-propanal-acetal and potassium iodide in a solution of ethyl alcohol, according to the general method of Wohl.[18]

The second attempt was in a measure successful, although the yields were small. The chlorine compound was refluxed with

sodium iodide in an acetone solution and did give a small per cent of substitution, although here again the amount obtained was too small to work with to advantage. This method would no doubt have proved successful on a larger scale, but was abandoned due to lack of time for the preparation of the beta-chloro-prop[illegible]nal acetal in sufficient quantities for further experiment.

EXPERIMENTAL

A. Preparation of Beta-Naphtho-dihydro-furane.



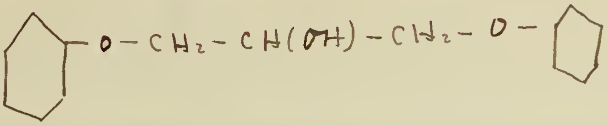
The above compound was prepared by the dehydration of beta-hydroxyethyl-beta-naphthyl ether by means of phosphorus pentoxide in a toluene solution. The alcohol-ether for dehydration was prepared by the common method of treating sodium naphtholate with ethylene chlorohydrine. Eighty-two grams of this alcohol-ether were dissolved in two hundred cubic centimeters of dry toluene and twenty-five grams of phosphorus pentoxide added in small portions with shaking, in order to avoid the formation of a cake and endanger breakage of the flask. The flask was then placed under a reflux condenser and the mixture refluxed for about an hour, after which the product was extracted with ether, washed with alkali, and distilled. The product resulted in a very dark, viscous oil of only about one per cent of the theory yield.

N_D^{33} 1.482; d_{30} 1.007

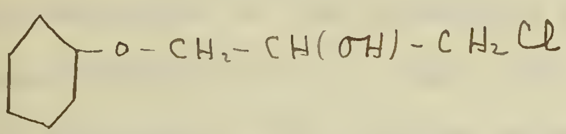
Subs. .2319; CO_2 451.2 cc.(32.5°: 742.5 mm.)

Calc. for $C_{12}H_{10}O$: C 84.8. Found 86.2.

B. Preparation of the symmetrical beta-hydroxy propyl-diphenyl ether



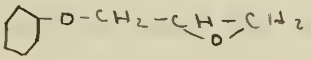
This compound resulted as a by-product in the preparation of gamma-chloro beta-hydroxy propyl phenyl ether.

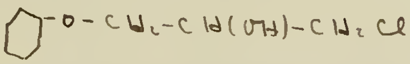


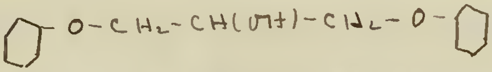
It was prepared by adding a cold solution of sodium phenolate to a cold solution of 1, 3 dichlorohydrine in absolute alcohol in molacular amounts. After refluxing three hours most of the alcohol was distilled off, water added, and the product extracted with ether. The ether extract was washed with alkali, then with water to remove the alkali, and dried with calcium chloride. Upon fractionation the following products were obtained:

12 gms. epichlorohydrine

40 " dichlorohydrine

17 "  B.P. 146°C - 30mm.

18 "  B.P. 174°-6° - 35mm

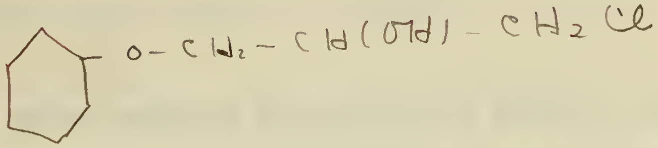
25 " 

The diphenyl ether was recrystallized from benzene and gave a pure white fine grained solid melting at 81°-81.5°C.

Subs. 0.2474; CO_2 479.6 cc.(281°, 746.6 mm.)

Calc. for $C_{15}H_{16}O_3$: C 73.77. Found 73.44.

C. Preparation of gamma-chloro-betal-hydroxy propyl phenyl ether.



Two methods were used, the first being that given above using sodium phenolate and 1, 3 dichlorohydrine. The second method[19] was that of treating free phenol with epichlorohydrine. The only variation of the procedure given in the literature was that sealed tubes in an oil bath were used instead of the autoclave as suggested. The charged tubes were held at a temperature of 160° C. for forty hours and the contents then fractionated under diminished pressure. Five runs were made, each charge being twenty-four grams of phenol and twenty grams of epichlorohydrine. Upon combining the dark brown reaction mixtures and fractionating, the following three fractions were obtained:

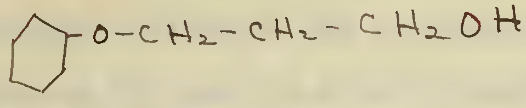
1. Low boiling up to 100° C. at 12 mm. consisting of unchanged epichlorohydrine and phenol.

2. Sixty grams of the desired product boiling at 150°-155° C. at 12 mm.

3. High boiling residue which was probably the diphenyl ether.

The second fraction is very viscous and colorless, possessing a disagreeable rancid odor and a very bitter taste. When touched to the tongue it apparently has the property to some degree of a local anaesthetic.

D. Oxidation of gamma-hydroxy propyl phenyl ether.



Various attempts were made, as pointed out above, to oxidize this compound to the aldehyde, the following agents being employed: potassium permanganate, potassium dichromate, and nitrogen tetroxide.

1. Potassium permanganate oxidation.

The alcohol-ether was dissolved in a little more than its own volume of concentrated sulphuric acid in an ice-pack with constant stirring and the potassium permanganate, in a minimum amount of water, added slowly. The reaction mixture became quite warm apparently and much charring resulted. After the course of an hour, the flask was removed from the ice pack, water was added, and the product extracted with ether. The ether layer was separated, washed with dilute alkali and then with water, dried with calcium chloride, and fractionated.

The result of this oxidation was a very large per cent of tars and some acrolein, indicating that the compound had been broken at the oxygen linkage.

2. Potassium dichromate oxidation.

The same general procedure was used as with the permanganate. Various concentrations of acid were used, but, as above, the result seemed always to be quite complete oxidation to the formation of tars and acrolein or else unchanged alcohol-ether.

3. Nitrogen-tetroxide oxidation[20].

The nitrogen tetroxide was prepared by heating dry lead nitrate and condensing the gas in a coil cooled by an ice pack. The alcohol-ether in the first attempt was placed in a chloroform solution at room temperature and the liquid nitrogen tetroxide added. The reaction was very violent and resulted in an explosion, that burst the container with quite an appreciable force. The succeeding oxidations were carried out at a temperature of -15° C. obtained by an ice-salt solution. The extreme point of difficulty in the method is to have all materials and apparatus dry. If moisture is present concentrated nitric acid is formed, which always gives trouble upon subsequent distillation, a very violent oxidation ensueing that will usually break the flask and result in the loss of all materials involved. No very satisfactory results were obtained by this method, the principal products being tars, acrolein, and unchanged material.

E. Preparation of beta-chloro-propanal acetal.

The acrolein for this synthesis was prepared by the method of Wohl and Mylo as improved by E. J. Witzemann[21], the general procedure being to distill glycerol off anhydrous magnesium sulphate, the yield of crude acrolein being about forty per cent of the theory.

As previously pointed out the method of Wohl[16] was used for the acetal. Two volumes of absolute alcohol were cooled in an ice pack and then saturated with dry hydrochloric acid gas.

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

A stirring apparatus was attached and one volume of dry acrolein dropped in very slowly. Stirring was continued for about one-half hour after the aldehyde had been added, The acetal separates as a heavy viscous oily layer on the bottom, a lighter layer remaining on the surface, from which more acetal can be obtained by passing in more dry hydrogen chloride. The product was freed from hydrochloric acid by adding calcium carbonate until neutral to litmus and then from alcohol by washing with water. (Extreme care must be taken to remove all the hydrochloric acid before adding water, else the acetal group will be saponified, resulting in the formation of ethyl alcohol and the free beta-chlor-propanal.) The product was then dried with potassium carbonate and fractionated, the acetal distilling at 74° C. under 20 mm. pressure. The yield was about 65 per cent of the theory.

F. Beta-bromo-propanal acetal.[17]

A small amount of the bromo acetal was prepared by the same general method. Care must be taken that no free bromine be carried over with the hydrogen bromide while saturating the absolute alcohol, lest the alpha-beta-dibromo addition compound be formed.

If the hydrobromic acid gas is generated by dropping concentrated sulphuric acid into constant boiling hydrobromic acid, as was done in this case, the bromine can be very easily absorbed by an intermediate flask containing some dry anthracene.

G. Beta-iodo-propanal-acetal.[18]

1. The first attempt consisted in heating in a bomb tube for ten hours at 100° C. ten grams of the beta-chloro-propanal acetal and twelve grams of potassium iodide in fifty cubic centimeters of ethyl alcohol as a solvent. The alcohol was evaporated and water added. After extracting with ether, washing with dilute sodium hydroxide and drying with potassium carbonate, the product was distilled, but proved to be entirely the unchanged chlorine compound.

2. In the second case, one tenth mol of each of the chloro-acetal and sodium iodide were placed in thirty cubic centimeters of acetone as a solvent and refluxed for two hours. The acetone was distilled, water added, and the product extracted with ether. The extract was washed with dilute sodium hydroxide, dried with potassium carbonate and distilled. The product was for the most part unchanged beta-chloro-propanal acetal, but a very small fraction came over at 80° C. and 55 mm., indicating that some substitution had taken place.

SUMMARY

1. Beta-naphtho-dihydro-furane was prepared by a similar method used for the synthesis of the corresponding benzene compound from phenol and ethylene chlorohydrine; namely, coumarane.

2. The symmetrical beta-hydroxy propyl-diphenyl-ether was prepared by the use of sodium phenolate and 1, 3 dichlorohydrine.

3. Gamma-chloro-beta hydroxy propyl-phenyl ether was prepared from (a) epichlorohydrine and free phenol and (b) sodium phenolate and 1, 3 dichlorohydrine.

4. Attempts to prepare beta-methylene coumarane by dehydration of gamma-chloro-beta-hydroxy propyl phenyl ether and subsequent treatment with alcoholic potash were unsuccessful.

5. Beta-chromene could not be prepared by dehydration of the enolic form of the aldehyde resulting from the oxidation of gamma-hydroxy propyl-phenyl ether.

6. Beta-chloro-propanal acetal, prepared according to the method of Wohl[16], could not be made to react with sodium phenolate to split out sodium chloride as we should expect.

7. Beta-iodo-propanal acetal was obtained by replacement of chlorine by iodine, but in an insufficient quantity with which to work.

8. Beta-bromo-propanal acetal was also obtained but in too small a quantity to treat with sodium phenolate.

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